97. The method of claim 72, wherein the complexity of the labeled nucleic acid probe is greater than about 200 kb.--

REMARKS

Entry of the foregoing, reexamination and reconsideration of the above-identified application is respectfully requested.

Claim 72 has been amended to incorporate the recitation from dependent claim 87 and recite that the target chromosomal material is interphase chromosomal DNA. Claim 87 has, therefore, been deleted. Claim 72 has further been amended to recite that "the nucleic acid probe is substantially free of repetitive segments which are complementary to repetitive segments in the target interphase chromosomal material." Support for this recitation may be found at the very least at page 26, lines 12-16. No new matter has been added.

Claims 95-97 have also been added. Claim 95 has been added to recite detection of a chromosome 21 rearrangement. Support for this claim may be found at the very least in Example IX, beginning on page 130, and in Figure 4G. Claim 96 has been added to recite that fragments substantially complementary to repetitive segments in the target interphase chromosomal material have been removed from the labeled nucleic acid probe. Support for this claim may be found at the very least at page 26, lines 17-25, and in Section II, beginning on page 26, line 3. Claim 97 has been added to recite that the complexity of the

labeled nucleic acid probe is greater than about 200 kb. Support for this claim may be found at the very least at page 44, lines 6-14. No new matter has been added by these new claims.

Applicants acknowledge the objection to the color drawings. Upon indication of allowable subject matter, applicants will attend to this objection and either substitute black and white drawings or submit an appropriate petition.

Claim 94 has been rejected under 35 U.S.C. §112, first paragraph, as the disclosure is allegedly enabling only for claims limited to retinoblastoma rearrangement detection wherein there is used the specific primers showing chromosomal rearrangement involving chromosomes 13 and 21, as shown in Example IX of the specification. To expedite prosecution in this application and to overcome this rejection under §112(1), claim 94 has been deleted in favor of new claim 95 to recite detection of a chromosome 21 rearrangement. Withdrawal of this rejection is thus believed to be in order.

Claims 72-94 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over Weissman et al. This rejection, as applied to the claims as amended, is respectfully traversed.

Claim 72 now recites that the target chromosomal material is interphase chromosomal DNA. Weissman et al fails to disclose or even suggest a method of staining target interphase chromosomal material. By contrast, Weissman discloses only mapping to metaphase spreads (*see,* for example, Figure 5, Section VI and Example XI). That interphase

chromosomal material could be reliably stained in a method as claimed is in no way taught by Weissman.

Withdrawal of this rejection is thus respectfully requested and believed to be in order.

Claims 48-94 have been rejected under 35 U.S.C. §103(a) as allegedly being unpatentable over U.S. Patent No. 5,447,841, which is asserted to be prior art under 35 U.S.C. §102(e). This rejection is respectfully traversed.

It is respectfully believed that the invention as claimed herein finds support in the originally filed application from which priority is claimed, i.e., Application Serial No. 819,314, filed January 16, 1986 ("the '314 application"). This is the same application from which U.S. Patent No. 5,447,841 claims priority. U.S. Patent No. 5,447,841 thus is not prior art under §102(e) to the instant application.

More specifically, a method of staining target interphase chromosomal material as claimed is sufficiently described in the '314 application to satisfy the requirements of 35 U.S.C. §112, first paragraph. The function of the description requirement of §112 is to ensure that the applicant had possession, as of the filing date of his application, of the specific subject matter later claimed by him. It is required that the specification describe the invention sufficiently for those of ordinary skill in the art to recognize that the applicant invented the subject matter he now claims. Behr v. Talbot, 27 USPQ2d 1401, 1407 (BPAI 1992). Ex

Parte Raible, 8 USPQ2d 1709, 1710 (PTO Bd App & Int 1988). Ex Parte Harvey, 3 USPQ2d 1626, 1627 (PTO Bd. App. & Int. 1987). This requirement is met for the claimed invention in the '314 application.

The '314 application states at page 8, lines 6-12:

> The invention includes methods and compositions for staining chromosomes. In particular, chromosome specific staining reagents are provided which comprise heterogeneous mixtures of labeled nucleic acid fragments having substantial portions of substantially complementary base sequences to the chromosomal DNA for which specific staining is desired.

The '314 application further states:

> As discussed more fully below, preferably the heterogeneous mixtures are substantially free from so-called repetitive sequences, both the tandem variety and the interspersed variety (see Hood et al., Molecular Biology of Eucaryotic Cells (Benjamin/Cummings Publishing Company, Menlo Park, California, 1975) for an explanation of repetitive sequences).

Nucleic acid probes from which repeats have been removed and the use of blocking nucleic acid are described at the very least at page 10, lines 1-10; page 19, line 14 to page 23, line 23. The staining of interphase chromosomal DNA is also described at the very least at page 10, lines 11-16; page 11, line 24 to page 12, line 2; and page 36, lines 6-9.

The use of a "labeled nucleic acid probe having a complexity greater than about 40 kb" finds support and is sufficiently described in the '314 application to satisfy the requirements of 35 U.S.C. §112, first paragraph. At the very least, the '314 application states:

> In one preferred embodiment where the heterogeneous mixture is generated on a fragment-by-fragment basis, the chromosomal DNA is initially cloned in long sequences, e.g., 35-45 kilobases in cosmids, or like vector. After amplification the inserts are cut into smaller fragments and labeled for formation to a heterogeneous mixture. In this embodiment, the chromosomal binding sites of the fragments are clustered in the chromosomal regions complementary to the cloned "parent" nucleic acid sequence. Fluorescent signals from such clusters are more readily detected than signals from an equivalent amount of label dispersed over the entire chromosome. In this embodiment, the clusters are substantially uniformly distributed over the chromosome. (Page 13, line 23 - page 14, line 11).

The application thus teaches the use of one or more cosmids, each having a complexity of about 35-45 kb. This application thus sufficiently describes a labeled nucleic acid probe "having a complexity greater than about 40 kb," as now claimed.

Moreover, the Examples employ labeled probes having a complexity of at least 40 kb as now claimed. Example V, for example, describes probes having 100 clones, each of 3 kb. *See*, for example, page 34, line 24 to page 38, line 12.

Still further, original claim 5, for example, recites that "labeled nucleic acid fragments are derived from substantially equal amounts of between about 10-1000 distinct cloned inserts each having a length within the range of between about 20-45 kilobases."

Similarly, support for new claim 97, which recites that the complexity of the probe is greater than about 200 kb, is found in the '314 application. As previously stated,

original claim 5, for example, recites that "labeled nucleic acid fragments are derived from substantially equal amounts of between about 10-1000 distinct cloned inserts each having a length within the range of between about 20-45 kilobases." Taking the lower limit of each range, the lower limit of the claimed complexity is obtained, i.e., 10 distinct cloned inserts each having a length of about 20 provides a probe complexity of 200 kb. Complexities of greater than about 200 kb are obtained using the remainder of the disclosed ranges.

That the dependent claims are supported by the priority applications is evident by comparing the dependent claims with claims 1-17 of U.S. Patent No. 5,447,841.

Because of the '314 application's description, including the example and claims, the '314 application provides written description for the now claimed subject matter. As stated by the Court in In re Wertheim, 191 USPQ 90, 98 (CCPA 1976):

> In the context of *this* invention, in light of the description of the invention as employing solids contents within the range of 25-60% along with specific embodiments of 36% and 50%, we are of the opinion that, as a factual matter, persons skilled in the art would consider processes employing a 35-60% solids content range to be part of appellants' invention and would be led by the Swiss disclosure so to conclude.

Moreover, as found acceptable by the Court in In re Johnson, 194 USPQ 187, 196 (CCPA 1977), applicants here are claiming a subgenus (greater than about 40 kb) of a genus (greater than about 35 kb) fully disclosed and exemplified in the '314 application. As

such, the written description requirement is met and applicants are entitled to priority of the '314 application.

In view of the above, U.S. Patent No. 5,447,841 is not prior art to applicants under §102(e). The rejection under §103(a) is thus improper and should be withdrawn. Withdrawal of the rejection is respectfully requested.

Claims 48-71 have been rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over U.S. Patent No. 5,447,841. It is respectfully requested that this rejection be held in abeyance. Upon indication of otherwise allowable subject matter, submission of a terminal disclaimer will be considered by applicants.

Further and favorable action in the form of a Notice of Allowance is respectfully requested.

In the event that there are any questions relating to this response, or to the application in general, it would be appreciated if the Examiner would telephone the undersigned attorney concerning such questions so that prosecution of this application may be expedited.

Respectfully submitted,

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